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14. ABSTRACT Here we report major findings for our project aimed at studying the expression of Discoidin Domain Receptors (DDRs) in breast cancer (BrCa) tissues and their functional contribution to the formation of BrCa bone metastases. We also aim at testing the feasibility of targeting DDRs for the treatment BrCa bone metastases. During the first funding period, we performed immunohistochemical analysis of DDR1 in 120 samples of invasive BrCa cases with different molecular subtypes and found a significant inverse association between cytoplasmic DDR1 localization and progesterone receptor expression in ER+ tumors. However, the limited number of primary tumors with match bone metastases compromised significance. In this period, we expanded the tissue collection to 42 new cases, which will be analyzed for DDR expression in the next period. In the period of this report, we tested the effect of a new small molecule DDR1 kinase inhibitor in a model of intraosseous tumor growth using MCF7-Luc BrCa cells in mice supplemented with estrogen. These studies showed no significant effect of the inhibitor on intraosseous tumor burden between treated and untreated mice. A limitation of this study was the significant formation of bone observed in mice treated with estrogen, which limited tumor growth, and possibly affected tumor response to the inhibitor. In the next period, we will utilize MDA-MB-231 cells with modified DDR expression in the intraosseous tumor model. We will also follow the proposed Tasks and investigate the role of tumor-associated DDRs on the regulation of pro- and anti-osteolytic genes *in vitro*.

15. SUBJECT TERMS
Breast cancer, bone metastasis, discoidin domain receptors, kinases, targeted therapies, immunohistochemistry

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1. INTRODUCTION

Different treatments are currently used to treat bone metastasis, the main cause of morbidity and mortality in patients with advanced breast cancer (BrCa). However, although currently available therapies can be effective to relieve pain, prevent complications, and improve quality of life in these patients, are not curative. The identification of novel molecules involved in the establishment and expansion of BrCa metastatic cells within the bone is, therefore, crucial for the development of new prognostic biomarkers and therapeutic agents to prevent and/or inhibit skeletal metastases. Discoidin domain receptors (DDRs) are expressed in invasive BrCa and represent the only receptor tyrosine kinases (RTKs) that uniquely signal in response to collagen, a major organic component of the bone microenvironment. Based on these facts, the purpose of the research proposed in this application is to test our hypothesis that DDRs mediate the survival of metastatic BrCa cells within the skeletal niche and consequently represent promising targets for intervention in BrCa patients with bone metastasis. The scope of research involves the analysis of DDR expression in primary tumor and bone metastatic tissues from BrCa patients, the evaluation of therapeutic efficacy of DDR inhibition in a preclinical model of intraosseous BrCa growth, and the study of tumor-derived DDRs' role in the regulation of BrCa pro-osteolytic programs using *in vitro* systems.

2. KEYWORDS

Discoidin domain receptors, breast cancer, bone metastasis, receptor tyrosine kinases, collagen, biomarkers, targeted therapy.

3. ACCOMPLISHMENTS

- **What were the major goals of the project?**

Specific Aim 1. To conduct a histopathological analysis of DDR expression in samples of primary BrCa tissues with different subtypes and their matching bone metastasis.

Task 1: Select BrCa tissues for analyses and construct tissue microarrays (TMAs).

Task 2: Analyses of DDR expression.

Specific Aim 2. To evaluate the therapeutic efficacy of DDR inhibition in a preclinical xenograft model of intraosseous BrCa growth.

Task 1: Analyze DDR expression/activation and generate modified BrCa cell lines.

Task 2: Animal Studies.

Specific Aim 3. To investigate the role of tumor-derived DDRs in regulation of BrCa pro-osteolytic programs in cell culture systems.

Task 1: Evaluate role of DDRs in regulation of pro-osteolytic factors.

Task 2: Conduct *in vitro* osteoclastogenesis studies.

- **What was accomplished under these goals?**

1) Major activities:

Specific Aim 1.

Task 1: Select BrCa tissues for analyses and construct tissue microarrays (TMAs), and **Task 2**: Analyses of DDR expression.

In the last funding period, we found a significant association between DDR1 protein localization and PR status, namely cytoplasmic DDR1 was significantly associated with negative PR expression (p=0.015). We also reported that expression of cytoplasmic DDR1 was associated with shorter time to recurrence or death when compared to cytoplasmic + membranous staining (Hazard Ratio [HR] 2.03, 95% confidence interval [CI] 1.12-3.69, p=0.021). Membranous DDR1 was associated with shorter time to recurrence or death compared to cytoplasmic + membranous DDR1 staining (HR 2.22, 95% CI 1.12-4.37, p=0.022). However, from the 120 cases of primary invasive carcinoma analyzed, 16 cases had presence of bone metastasis. These cases were stained for DDR1 to determine whether DDR1 expression in the primary tumor was associated with bone metastasis. However, due to the limited number of cases, during the year of this report we devoted efforts to identify additional primary invasive carcinomas and their corresponding distant metastasis from the same patients. This involved comprehensive searches in the surgical pathology databases form our institution and retrieval of blocks, some of which were stored in a different location. We encountered several problems which were overcome. These included the fact that in most cases, metastatic breast cancer to distant sites are minimally biopsied, which resulted in limited tissue available for immunostaining, the fact that several cases have been returned to other institutions, and because breast cancer metastasizes late (sometimes even 20 years) after primary tumor diagnosis, several primary tumors were over 15 years old. Despite these issues, we were successful in retrieving the cases described in detail in the table below (next page)

Case	Type	Age at primary	Age at met	Histological type	Tumor Grade	Site of Bone Met
1	Metastasis	42	51	Lobular		paraspinal
	Primary			Lobular		
	Primary			Lobular		
2	Metastasis	61	72	Ductal		Bone
	Primary			Ductal	2	
3	Metastasis	72	77	Lobular		Left ileum
	Primary			Lobular	2	
	Primary			Lobular		
4	Metastasis	43	43	Ductal		Left iliac
	Primary			Ductal		
	Primary			Micropapillary	3	
5	Metastasis	62	62	Ductal		Left sacrum
	Primary			Ductal	2	
6	Metastasis	74	78	Ductal		R. ilium
	Primary			Mucinous	2	
7	Metastasis	41	67	Ductal	2	Left 5th rib
8	Metastasis	49	51			BM
9	Metastasis	49	73	Ductal		L. femoral head
10	Metastasis	58	60	Ductal		T9 vertebrae
	Primary			Ductal	3	
	Primary			Ductal		
11	Metastasis	42	44	Ductal		Lumbar vertebrae
	Primary			Ductal	3	
	Primary			Ductal	3	
	Primary			Ductal	3	
12	Metastasis	38	40	Ductal		R. femoral head
	Primary			Ductal	3	
13	Metastasis	49	49			L. distal humerous
	Primary			Ductal	1	
14	Metastasis	44	52	Lobular		Bone
	Primary			Lobular	1	
15	Metastasis	31	31			bone
	Primary			Ductal	3	
16	Metastasis	57	69			R. ilium
	Primary			Ductal	2	
17	Metastasis	49	61			R. Ilium
	Primary					
18	Metastasis	65	65	Lobular		R. Ileum
	Primary			Lobular	1	
19	Metastasis	65	65			T10
	Primary			Micropapillary	1	
20	Metastasis	73	73	Lobular		R. Ileum
	Primary			Lobular		

Continues in next page

Case	Type	Age at primary	Age at met	Histological type	Tumor Grade	Site of Bone Met
21	Metastasis	68	75	Lobular		L. iliac
	Primary			Lobular	2	
22	Metastasis	57	57			R. iliac
23	Metastasis	57	57			R. Iliac
	Primary			Ductal and lobular	1	
24	Metastasis	69	69			T9
	Primary			Ductal and lobular		
	Primary			Micropapillary	3	
24	Metastasis	53	53			Left ilium
	Primary			Micropapillary	3	
26	Metastasis	35	57			T8
27	Metastasis	59	59			Left ilium
	Primary			Lobular	1	
28	Metastasis	63	63			bone
	Primary			Lobular	2	
29	Metastasis	34	37			left ischium
	Primary			Ductal and lobular	2	
	Primary					
30	Metastasis	41	50			Epidural/T-6
	Primary			Ductal	2	
	Primary			Ductal	2	
31	Metastasis	44	82	Ductal		sternum
32	Metastasis	54	54	Ductal		L5
	Primary			Ductal	3	
33	Metastasis	42	56			R. ilium
	Primary			Ductal	2	
34	Metastasis	44	73			R. ilium, L Sacrum
35	Metastasis	48	48	Lobular		bone
	Primary			Lobular	1	
36	Metastasis	57	62	ductal and lobular		T8/epidural
37	Metastasis	57	57	Lobular		L1
	Primary			Lobular	1	
38	Metastasis	49	52	Ductal		Femoral head
	Primary			Ductal	1	
39	Metastasis	77	78	Lobular		R. Ileum
	Primary			Lobular	2	
40	Metastasis	38	39	Ductal		R. Ileum
	Primary			Ductal	3	
42	Metastasis		66	Invasive papillary		Ischial

We are also retrieving the treatment and follow up information. We have the blocks on 13 primaries and metastatic carcinomas with sufficient tissue for further analyses and are preparing sections for immunostaining with anti-DDR antibodies, collagen Ia, LoxL2, and Runx2, as planned in the original aims. We will be conducting these analyses in the next cycle.

Specific Aim 2.

Task 1: Analyze DDR expression/activation and generate modified BrCa cell lines.

This has been accomplished and reported in the 2017 Report. Briefly, we characterized expression of DDRs in multiple breast cancer cell lines with the focus on identifying cells with DDR1 expression and capable of growing within bone in mouse models. In particular, estrogen receptor (ER) positive cells. The rationale for this phenotype stems from the well-established observation that most women with bone metastatic disease harbor breast tumors that are ER+. Therefore, we proposed to use the ER+ MCF7 breast cancer cell line to test our hypothesis. We showed in the previous report the identification of luciferase-labeled ER+ MCF7 cell line (referred to as MCF7-Luc) that is positive for DDR1 expression. This cell line was also used in the studies to test the selective DDR1 kinase inhibitor (KI), referred to as **Compound A**. We reported the properties of this inhibitor in the 2017 report, including its ability to inhibit it DDR1 activation in MCF7-Luc cells.

Task 2: Animal Studies.

To study the effect of the DDR1 KI, we used direct injection of tumor cells into the mouse tibiae (intratibial model). This xenograft model allows the establishment of intraosseous tumor lesions by bypassing the metastatic cascade, and thus focus on the factors that regulate intraosseous tumor growth including interactions with the bone microenvironment. In addition, the intratibial model offers the opportunity to study the effects of anti-tumor therapies in bone metastases and of therapies designed to minimize the damaging effects of cancer cells to the bone, including osteolysis (bone destruction) and bone pain. Using the intratibial model, as proposed in our original application, we conducted a preliminary animal study to test the ability of the MCF7-Luc cells to produce tumors when inoculated into the tibiae of immunodeficient mice, under the approved IACUC protocol covered by this award. The results of this study were reported in the previous report. Briefly, we inoculated $1x10^5$ MCF-7-Luc cells/mouse into the tibiae of female nude mice without estrogen supplementation or in mice implanted subcutaneously with 0.18 mg/90-day extended release 17β-estradiol pellets. Tumor growth was evaluated by bioluminescence (BLI). We reported that mice inoculated with MCF7-Luc cells without estrogen supplementation showed no BLI signal after 4 weeks. In contrast, all mice receiving 17β-estradiol supplementation, displayed strong BLI signal, consistent with intraosseous growth of MCF7-Luc cells. This result provided the impetus to conduct a therapeutic study using the selective DDR1 KI provided by Roche.

Protocol Details: **Figure 1** describes the overall schematic of the study conducted to test Compound A. The protocol included two experimental groups of mice (n=9): Compound A- and vehicle-treated mice. Compound A was given daily, IP, at a dose of 90 mg/Kg as per Roche recommendation. Compound A was dissolved in 0.3% Tween-80, 0.9% NaCl. This solution was used as vehicle. Prior to tumor cell inoculation, 17β-

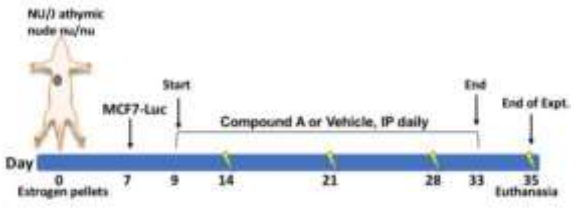

Fig. 1. Schematic of the animal protocol

estradiol 0.18 mg 90-day release pellets were implanted in the mice. A week later, mice were inoculated intratibially with $1X10^5$ cells per mouse. Treatment with Compound A or vehicle were initiated two days after tumor cell inoculation and administered daily, IP. Mice were subjected to bioluminescence imaging (BLI) every week, starting 5 days after treatment (=7 days after tumor injection), for a total of 4 times. To this end, mice were injected intraperitoneally with 150 mg/g D-luciferin in PBS, anesthetized with 2.5% isofluorane, and then imaged. For X-ray imaging, mice were imaged with a Bruker's In-Vivo Xtreme optical and x-ray small animal imaging system. Regions of interest (ROI) from displayed images were identified and were quantified as total photon counts or photons/s using Living Image® software 4.0 (Caliper, Alameda, CA.).

Data Analyses: For BLI quantitation of tumor growth, tumor sizes were calculated using the sum of total photon flux emission (photons/second/mm2) in the regions of interest (ROI) covering the entire tumors. The tumor growth rates across four-time points (Week 1 to 4) were compared using the linear mixed-effects model after tumor sizes were log-transformed. The model allowed for subject-specific baseline tumor size and tumor growth rate considering the correlation between time-dependent observations within the same subject. Tumor sizes were calculated using the sum of total photon flux emission (photons/second/mm2) in the regions of interest (ROI) covering the entire tumors. The tumor growth rates across four-time points (Week 1 to 4) were compared using the linear mixed-effects model after tumor sizes were log-transformed. The model allowed for subject-specific baseline tumor size and tumor growth rate considering the correlation between time-dependent observations within the same subject. To assess the tumor size at the last time point (Week 4), unpaired t-test was used after log-transformation. All data were summarized as mean ± standard error of mean (SEM) under a log-normal distribution.

For analyses of tumor burden by histomorphometry, ex-vivo tibia were fixed in 4% paraformaldehyde and imbedded in paraffin blocks. Paraffin sections (5 μm) derived from bone tumors were immunostained with Pan-cytokeratin and counterstained with hematoxylin. Digital photomicrographs of the entire histological section were captured at 5× magnification and stored as jpeg files. The entire image was then reconstructed using Adobe Photoshop. Tumor tissue (cytokeratin positive areas) and trabecular bone were isolated into separate layers and separately thresholded to black. The whole tissue cross sectional area (considered 100%) was then highlighted and the area occupied by either tumor or bone was automatically calculated. In addition, sections were stained for expression of DDR1, using specific antibodies.

Results: Analyses of BLI: **Figure 2** shows the results of the quantitative analyses of BLI as a function of time. These data showed no statistical significance between mice treated with Compound A and vehicle control. **Figure 3**, shows the BLI image of mice at week 4. **Figure 4** shows the analyses of the BLI data at week 4. These analyses showed no statistical significance, indicating that there is no evident effect of Compound A on tumor burden in this model system, using MCF7 cells. There were no signs of toxicity, as determined by the weight and overall health of the mice. After euthanasia, bones were processed for histomorphometry by staining the tumors with H&E and cytokeratin (**Fig. 5**). H&E stained bone sections revealed cluster of tumor cells growing with bone marrow cavities (**Fig. 6**). Interestingly, examination of the sections also revealed abundant areas of dense bone tissue with reduced bone marrow spaces (**Fig. 6**, black arrow, next page), suggestive of an osteoblastic response, possibly as a consequence of estrogen supplementation. Histomorphometry analyses of tumor burden, by measuring areas positive for cytokeratin, showed that these data agreed with the finding obtained by BLI, namely that there was no statistical difference in tumor burden between untreated and treated groups.

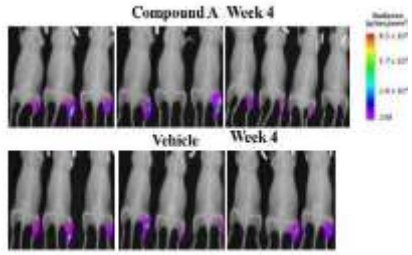

Fig. 3. BLI of mice harboring MCF7-Luc tumors at 4 weeks.

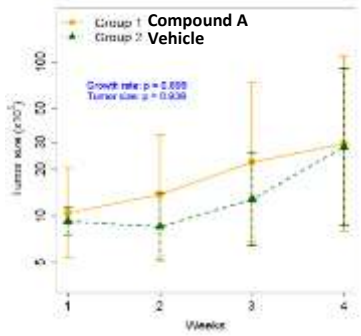

Fig. 2. Time dependent quantitation of MCF7 intraosseous tumor burden by BLI in mice treated with Compound A or vehicle control. Tumor size at Week 4: Mean (95% CI). Compound A ($\times 10^5$ photons/second/mm2): 29.38 (7.91, 109.07); Vehicle ($\times 10^5$ photons/second/mm2): 28.05 (8.63, 91.19)

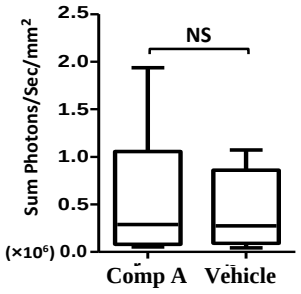

Fig. 4. Quantitation and statistical analyses of MCF7 intraosseous tumor burden by BLI at week 4 in untreated and treated mice. Wilcoxon matched-pairs signed rank test

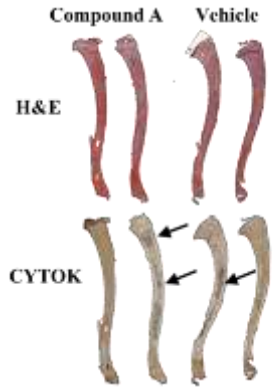

Fig. 5. Representatives images of bones processed for H&E and pan-cytokeratin (CYTOK). Arrows show areas with tumor.

We wished to verify that MCF7-Luc cells express DDR1 within the bone microenvironment. Therefore, we perform immunohistochemistry of bone tissue sections using antibodies that recognize only human DDR1. As shown in **Figure 7**, DDR1 is highly and broadly expressed in MCF7-Luc cells growing within bone, where it is mostly detected on the cell membrane, as expected. Unfortunately, due to the limitations of current available antibodies for detecting phosphorylated DDR1, we could not determine whether there is a difference in receptor activation, under these conditions. Thus, at present we cannot discern whether the DDR1 inhibitor is indeed targeting receptor activity.

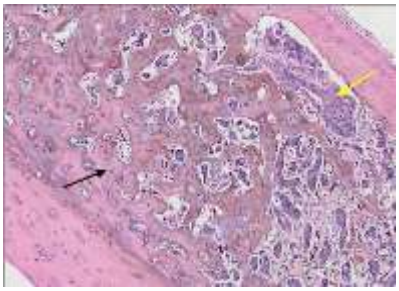

Fig. 6. H&E of bone sections from tibiae of mice harboring MCF7-Luc tumors (yellow arrow). Black arrow shows the dense bone matrix present cells growing with bone. Upper panel 20X and lower panel 40X.

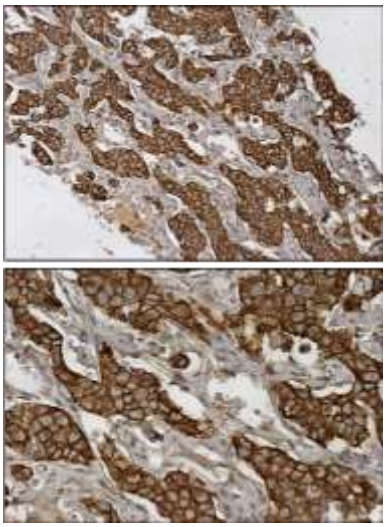

Fig. 7. Expression of DDR1 in MCF7-Luc cells growing with bone. Upper panel 20X and lower panel 40X.

Specific Aim 3.

Task 1: Evaluate role of DDRs in regulation of pro-osteolytic factors.

Nothing to report. We are initiating these studies.

Task 2: *In vitro* osteoclastogenesis studies.

Nothing to report. We are initiating these studies.

2) Specific objectives:

The objectives during the period covered by this report were:

a. Continue the identification of primary invasive breast carcinomas cases with matching bone metastases for analyses of DDR expression.

b. Conduct animal studies of intraosseous tumor growth to determine the efficacy of a selective DDR1 inhibitor.

3) Significant results or key outcomes:

Specific Aim 1, Tasks 1 and 2:

Specific Aim 2, Task 1 and 2: We examined the effect of a small molecule inhibitor of DDR1 (Compound A) on the growth of ER+ human breast cancer MCF7 cells. Based on these results we conclude, at this junction, that:

1. MCF7-Luc cells grow within mice tibiae only in the presence of 17β-estradiol. This is consistent with these cells being ER+.

2. MCF7-Luc express endogenous and functionally active DDR1 that is activated in response to collagen I.

3. Compound A, a selective DDR1 inhibitor, inhibits collagen-induced DDR1 activation in MCF7-Luc cells in vitro (previously reported).

4. Tibiae of mice inoculated with MCF7-Luc cells develop intraosseous tumor infiltrating into the bone marrow that are positive for DDR1.

5. Analyses of bones revealed significant areas of dense bone tissue with constricted bone marrow spaces, which may limit tumor expansion.

6. Treatment of mice with Compound A showed no evidence of anti-tumor effect when compared to untreated mice, as determined by quantitative imaging of tumors and histomorphometry.

Specific Aim 3, Task 1 and Task 2: Will be conducted in the new funding period

4) Other achievements:

Nothing to report.

- **What opportunities for training and professional development has the project provided?**

Nothing to report.

- **How were the results disseminated to communities of interest?**

Nothing to report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

For the next period, we plan to perform the following studies, as per the SOW:

Specific Aim 1, Tasks 1 and 2: We continue to build the set of cases to examine expression of DDRs in primary and bone metastatic breast cancer.

Specific Aim 2.

Task 1: We are generating MCF7-Luc cells with silenced expression of DDR1. This is ongoing. These cells will be used to assess the role of endogenous DDR1 on tumor growth. We identified several MDA-MB-231 cell lines (triple negative breast cancer cells), which are known to grow

within bone and induce osteolytic lesions. However, the luciferase labeled cells we obtained did not express endogenous DDR1 or DDR2. Therefore, we generated MDA-MB-231 with expression of recombinant DDR1b or DDR2. These cells are now being transduced to express luciferase.

Task 2: Due to the need of estrogen for MCF7 tumor growth, which results in significant de novo bone synthesis, the MCF7 tumor model is not ideal. Indeed, the abundant bone matrix, likely induced by the known effect of estrogen on bone synthesis, appears to reduce tumor burden within dense bone. This tumor load makes it difficult to evaluate therapeutic efficacy. Thus, at this junction, we cannot determine whether the lack of therapeutic effect was due to the limited tumor burden or availability of inhibitor within the dense bone microenvironment. To address the first issue, we will use ER- MDA-MB-231 cells, which do not require estrogen supplementation. We will address the role of DDRs by upregulation and downregulation. Based on these results, we will evaluate the effectiveness of the inhibitor in tumor extracts harvested from untreated and treated mice.

Specific Aim 3.

These studies will be initiated in the next period, as we reported.

Task 1: We will follow with the studies proposed in SOW examining the role of DDR activation on the expression of pro-osteolytic factors in the BrCa cells.

Task 2: We plan to conduct the studies proposed. Specifically, we will evaluate the role of conditioned media (CM) obtained from BrCa cells with defined/controlled DDR1 or DDR2 expression and activation on the regulation of osteoclastogenesis in murine pre-osteoclastic RAW264.7 and primary monocytic bone marrow cells. We will also compare relative gene expression of markers of osteoclast differentiation in BrCa with defined/controlled DDR1 or DDR2 expression/activation using real-time PCR. In addition, we will investigate the effect of BrCa-derived CM on osteoblast differentiation using mouse pre-osteoblastic MC3T3-E1 cells in mineralization assays and assess their effect on the expression of osteoblast differentiation markers.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Nothing to report.

5. CHANGES/PROBLEMS

As we described, we confirmed that the MCF7 system requires estrogen supplementation to grow within bone. However, we observed a secondary effect of estrogen on bone formation. This side effect could have impacted the extent of tumor burden. Therefore, we will focus on the osteolytic model of MDA-MB-231 cells.

Actual or anticipated problems or delays and actions or plans to resolve them

See above section.

- **Changes that had a significant impact on expenditures**

Nothing to report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

- **Significant changes in use or care of human subjects**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

Nothing to report.

- **Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. PRODUCTS

- **Publications, conference papers, and presentations**

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project? See Note below Table**

Name	Project Role	Nearest Person Months Worked	Contribution to the Project	Funding Support
Ricardo Daniel Bonfil[1]	Initiating PI	1.2	Design of experiments and data analyses	This grant
Rafael Fridman[2]	Initiating PI (9/17-present) Partnering PI (prior to 9/17)	0.72	Design of experiments and data analyses	This grant
Hyeong-Reh Kim[3]	Partnering PI (9/17-present)	0.79	Design of experiments and data analyses	This grant
Allen Saliganan	Research Assistant	6.6	Animal studies, immunohistochemical (IHC) assays	This grant
Anjum Sohail	Research Scientist	4.2	Expression/activation analysis of BrCa cells, analysis of pro-osteolytic factors	This grant
Celina Kleer	Co-I	0.6	Searches in the pathology databases, evaluation of histology and selection of tissue blocks. Scoring and analyses of IHC data obtained for TMA and association with	This grant (subcontract)

			histopathological features	
Maria E. Gonzalez	Research Associate	4.8	Selection of tissue blocks for processing, TMA construction, evaluation of IHC data	This grant (subcontract)

Note:
1. Dr. Bonfil, former Initiating PI, departed Wayne State University in August 2017. He is acting now as a Paid Consultant, as we reported at the time of his departure.
2. Dr. Fridman, former Partnering PI, became Initiating PI upon the departure of Dr. Bonfil.
3. Dr. Hyeong-Reh Kim became Partnering PI from September 2017.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Rafael Fridman, Initiating PI in this grant:

Idea Award with Special Focus, CA170568
PRCRP
"Disrupting Collagen-Mediated Pro-Survival Pathways in Pancreatic Cancer"
This application proposes to inhibit the Discoidin Domain Receptors with a single agent and in conjunction with drugs targeting RAS-MEK-ERK as a new possible treatment for PDAC. Specific Aim 1: Evaluate the Role of DDRs in Resistance to MEK Inhibition and their Effectiveness as Potential Therapeutic Targets in the KPC Mouse Model. Specific Aim 2: Establish the Anti-Tumor Effect of Single or Combinatorial Lethality of DDR1 Inhibition on Human PDX and Matched Organoid Cultures.
Role: PI
Status: Recommended for Funding

Dr. Hyeong-Reh Kim, Partnering PI

Nothing to report.

Celina Kleer, Co-Investigator in this grant:

Nothing to report.

- **What other organizations were involved as partners?**

Organization Name: Hoffmann-La Roche
Location of organization: Basel, Switzerland
Partner's contribution to the project: Supplied antibodies for DDR1 and a small molecule inhibitor for DDR1.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

Nothing to report.